別紙様式第2-1
番号5

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医薬部外品　研究報告　調査報告書
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識別番号・報告回数			報告日	第一報入手日 2004年10月21日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	人ハプトグロビン		研究報告の公表状況	DNV Consulting, UK/ February 2003	公表国 イギリス	
販売名（企業名）	ハプトグロビン注－ヨシトミ(ベネシス)					

研究報告の概要

本文書は、英国海綿状脳症諮問委員会（SEAC）の勧告をもとにして英国保健省から委託を受けた英国のコンサルタント会社のDet Norske Veritas（DNV）が、vCJDの伝達性病原体から血液及び血液製剤のレシピエントを守るために、vCJD発症者からの血液及び血液製剤のレシピエントの特定とリスク評価を行い、さらにリスク削減を目的にした手段の有効性を考察したものであり、2003年2月に最終報告として発行（DNVのHPには2004年4月に公表）された。

［目的］

本報告は、先に行われた1999年の報告を更新したもので、以下の目的を有している。

1）1998年以降に発行された研究論文を分析することによって、血液及び血液製剤の人の健康に対する1999年のリスク評価を更新すること。

2）以前には含まれていなかった血漿分画製剤を評価の対象に加えること。

3）CJD Incidents Panelがリスク評価を行い且つ汚染された可能性のある血液製剤の投与を受けたと考えられる患者に与えるべき助言を決定することができるように、ツールを提示すること。

1999年の報告と同じく、本報告の目的は、発症者からの血液が輸血によって伝播する可能性についての結論を得ることではなく、血液に感染性が存在するとの前提をもとにして検討を加えることである。

［前提条件］

文献等の評価をもとに、血液におけるvCJDの感染性の評価のために設定された前提条件は以下のとおりである。

1）vCJD発症者からの血液の静注投与による感染性は、ID50で表した場合、2 i/v ID50/ml人血液とし、その範囲は0.2から60 i/v ID50/ml人血液とする。

2）感染性は、潜伏期間を通して変わることがないと仮定する。ただし、最初が感染性が高くて潜伏期間中に漸次減少することも、また最初は低くて漸次上昇すると考えることも可能ではある。

3）血液成分の感染性は、文献に公表されたマウスの実験結果をもとに、全血で定義された感染性の値（2 i/v ID50/ml）とは異なると仮定する。

4）血漿分画製剤の感染性は、異なる2つのアプローチを使って行われ、本報告案についての議論の中でDNVに寄せられた科学的評価は、いずれのアプローチも科学的基盤のもとで正当であることを示している。

5）vCJD感染性の用量-反応作用は、直線的で閾値はないと仮定する。1 ID50の1投与は、感染の50%の可能性を有し（2 ID50もしくはそれ以上の1投与によって感染が成立）、感染の可能性は投与量に比例するとする。1年間の繰り返し投与の蓄積効果が付加されるとし、最初の1年以降の投与は無視する。さらに、血液に由来するvCJDの潜伏期間は、人成長ホルモンのCJD例に基づいて、中央値を15年間とし、潜伏期間の90%が5-30年の範囲にあるとする。

［結論］

1）潜伏期間中の人の血液中に存在すると考えられるvCJD感染性のリスクのレベルについて確たる予測を立てることは不可能である。現時点での我々の知識をもってしては、輸血または血漿分画製剤を通して感染が起こるか否かについて確たる結論を導き出すことは不可能であるし、またvCJDにこれまで感染したと考えられる人の数についても全く分からない。

2）血液中の感染性の証拠は、殆どが動物モデルの実験に基づいており、TSEに人工的に感染させた動物からの血液を同じ種の動物に脳内接種すると、感染性を有することを示したものであった。

3）感染性は、血漿と白血球を含むバフィーコートに存在するようにみえるが、他の血液成分においてもまた発生する可能性がある。いくつかの実験では、感染性が白血球含量に比例しているとの仮説とは一致しないような、血漿中の著しい高いレベルの感染性が示されている。

4）もし、vCJD感染者の血液が感染性を有していると仮定し、感染性のレベルが動物モデルで示唆された通りとすると、赤血球製剤、血小板または血漿の1ユニット中の感染レベルは感染を引き起こすに十分であると考えられる。そのため、感染血からのこれら製剤のいずれかの投与を受けた患者は、感染のリスクを有することになる。

使用上の注意記載状況・その他参考事項等

本報告は献血ヴェノグロブリン一IH ヨシトミを代表製剤として、研究報告している(識別番号 E-040000010、報告日 2004年11月19日)。

2. 重要な基本的注意

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2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

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5)特定の血漿分画製剤の感染性のレベルは、感染した血漿プールからのこれら製剤のレシピエントが負うリスクとみなされる。この導き出された結果は、極めて不確かなものであり、血漿画分における感染性のレベルやその分布から導かれる仮定によって大きく異なる。投与量、投与回数及び血漿プールサイズの全てが可能性としてのリスクに影響し、これらをもとにした以下の計算式が考案された。
1名のvCJD患者からの1ドネーションを含む血漿プールをもとに製造された血漿分画製剤について、投与された患者の年間累積感染性レベル（ID50）は以下によって計算できる。

$$I = An\sum_{i=1}^{c} Bi$$

I = 血漿分画製剤の感染性推定値（ID50/iuまたはID50/g蛋白）
A = プールサイズ補正係数。I値はプールサイズが20,000（特殊免疫グロブリンは350、アンチトロンビンは3,500）の場合を1とし、それ以外の場合には、濃縮または希釈される場合の投入サイズに比例した係数とする。
n = 該当プールにおける、後でvCJDを発症したドネーションの数。ただし、筋注IgGの場合のn値は7で割った数とする。
Bi = 投与量（g蛋白またはiu）。個々の投与は同じプールからのものと仮定する。
c = ある患者が後でvCJDを発症したドナーからのドネーションを含むプールからの製剤の投与を受けた回数（1年間における）

上記の計算式より、vCJD患者からの1ドネーションを含むプール血漿から製造された血漿分画製剤から1年の間に伝播されると計算される推定感染性レベルは以下のとおりである（血漿分画製剤はScottish National Blood Transfusion Processの製法で製造された場合であり、またTSEのクリアランスファクター（CF）については、当該製剤の各製造工程のCFのうち、最大のCFを当該製剤のCFとした場合についてである）。

製剤名	製剤の感染性（I）(ID50/g or ID50/iu)	投与量（B）	1投与当り感染性 (ID50/dose)	年間投与回数 (c)	年間累積感染性 (ID50/year)
アルブミン	1.4×10^-7 ID50/g蛋白	慢性疾患　225g	3.0×10^-5	6	1.8×10^-4
	1.4×10^-7 ID50/g蛋白	ショック/集中治療　90g	1.2×10^-5	1	1.2×10^-5
ノーマル免疫G	8.4×10^-6 ID50/g蛋白	免疫不全症に対する置換療法　静注42g	3.5×10^-4	20	7.1×10^-3
	8.4×10^-6 ID50/g蛋白	免疫疾患に対する治療　静注140g	1.2×10^-3	12	1.4×10^-2
	8.4×10^-6 ID50/g蛋白	上記以外のその他の使用　静注140g	2.1×10^-6	?	?
特殊免疫G	3.4×10^-3 ID50/g蛋白	抗D　筋注250mg	8.4×10^-4	2	1.7×10^-3
	3.4×10^-3 ID50/g蛋白	HB、破傷風　筋注250mg	8.4×10^-4	1	8.4×10^-4
	3.4×10^-3 ID50/g蛋白	狂犬病、水痘帯状疱疹　筋注250mg	8.4×10^-4	3	2.5×10^-3
血液凝固第IX因子高純度	7.1×10^-7 iv ID50/iu	1250 iu	8.9×10^-4	52	4.6×10^-2
血液凝固第IX因子中純度	5.3×10^-7 ID50/iu	1250 iu	6.7×10^-4	50	3.3×10^-2
アンチトロンビン	3.4×10^-5 ID50/iu	3000 iu	1.0×10^-1	6	6.1×10^-1
血液凝固第VIII因子中純度 Z8	1.7×10^-5 ID50/iu	2000 iu	3.4×10^-2	30	1.0
血液凝固第VIII因子高純度	7.1×10^-7 ID50/iu	2000 iu	1.4×10^-3	30	4.3×10^-2

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報告企業の意見	今後の対応	
本情報は、英国保健省から委託を受けた英国のコンサルタント会社のDet Norske Veritas (DNV) が、血液及び血液製剤の投与等によるvCJDの二次伝播を防ぐために、vCJD発症者からの血液及び血液製剤のレシピエントの特定とリスク評価を行ったものである。血漿分画製剤の感染リスクの評価を行うに当たって、文献の調査に基づいた前提条件が設定され、リスク評価のための計算方法が提示されている。 英国保健省は2004年9月21日に、後でvCJDを発症した患者からの血漿分画製剤を投与されたレシピエントへの通知を行ったことを公表している（報告日：2004年10月6日、識別番号：G-04000194）が、その根拠となった資料がDNVによる血漿分画製剤のvCJDリスク評価結果である。 現時点でvCJDが報告されているのは英国と、英国滞在歴のないvCJD患者についてはフランス、イタリア、アイルランドのみである。なお、これまで血漿分画製剤からのvCJD伝播は報告されていない。しかしながら、万一vCJD感染者の血液が原料に混入した場合には、血漿分画製剤の製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ないため、弊社においても血漿分画製剤の製造工程におけるTSEの感染性の低減に関する検証実験を行っている。	本剤の原料血漿の供給元の米国ではこれまでvCJD症例は報告されていない。従って、本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。	

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RISK ASSESSMENT OF EXPOSURE TO vCJD INFECTIVITY IN BLOOD AND BLOOD PRODUCTS

for

DEPARTMENT OF HEALTH

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Risk Assessment of Exposure to vCJD Infectivity in Blood and Blood Products

for

Department of Health

Approved by:.....
Philip J Comer
Business Leader
DNV Consulting

Job No. 716108
Revision D
February 2003

Risk Assessment of Exposure to vCJD Infectivity in Blood and Blood Products

Issue Log

Revision	Issue Date	Prepared by	Reviewed by	Approved by	Comments
0	18 January 2002	Mark Purcell	John Spouge/ Philip Comer	Philip Comer	This report draws significantly from DNV 1999 report C8288 rev 4.
A	3 April 2002	Mark Purcell	Philip Comer/ Graham Vernon	Philip Comer	Updated calculations; removed sections on societal sensitivity assessment & mitigation measures. Included discussion paper regarding the 3 approaches to assessing plasma derivative infectivity.
B	17 May 2002	Mark Purcell	Philip Comer	Philip Comer	Minor text amendments, plus update on platelets infectivity.
C	9 January 2003	Mark Purcell	Philip Comer Graham Vernon	Philip Comer	Includes revised calculations based on SNBTS product yield data rather than annual basis; inclusion of expert comments; updated literature review, updated calculator.
D (Final)	24 February 2003	Mark Purcell	Graham Vernon	Philip Comer	Incorporates final comments, together with updated calculations.

Management Summary

The Spongiform Encephalopathy Advisory Committee (SEAC) advised Government in 1997 that they should carry out risk assessments to inform decisions on any measures that may be necessary to protect recipients of blood and blood products from the transmissible agent of new variant Creutzfeldt Jacob Disease (vCJD). In response to this advice, DNV were commissioned to undertake a risk assessment study. The study evaluated the overall risk to patient groups, as well as identifying those patient groups at highest risk, and considered the benefits of measures aimed at reducing risks. The Final Report was issued in 1999.

This present report is an update of the previous study that has the following objectives:

- To update the 1999 risk assessment of blood and blood products to human health by analysing research papers published since 1998.
- To extend the original study to include any plasma derivatives not included before.
- To adapt the 1999 report to provide a tool that the CJD Incidents Panel can use to estimate possible risks and determine advice given to patients known to have received potentially contaminated blood products.

Whilst the available evidence for infectivity in blood is reviewed, and it is concluded that blood from people with vCJD may contain infectivity that could be transmitted through blood transfusions, this has not been proved conclusively, and *it is not the purpose of this assessment to provide an answer to this question.* The study is based on *the assumption* that infectivity is present in blood. Additional research has not changed this position since the 1999 report.

The study has considered the way in which blood is collected and processed, how the various blood components (red cells, fresh frozen plasma and platelets) and plasma derivatives (such as Factor VIII, Immunoglobulin (IgG) and albumin) are used for patient treatments. The level of infectivity in whole blood, the blood components and the plasma derivatives has been estimated as a reference case, and the range of possible values identified. A calculator has then been developed to provide a tool that the CJD Incidents Panel can use to estimate possible risks.

At each stage assumptions have to be made about the factors that characterise the infectivity and the way in which the disease develops. There is considerable uncertainty about many of these factors, and hence considerable uncertainty in the predicted results.

Conclusions

1. It is not possible to make any firm predictions about the level of risk from any vCJD infectivity that may be present in the blood of people incubating the disease. With our current level of knowledge, it is not possible to draw any firm conclusion as to whether or not infectivity can be transmitted through blood transfusions or plasma derivatives and the number of people who may have been infected with vCJD is simply not known.

2. The evidence for infectivity in blood is mostly based on experiments with animal models that have shown that blood from an animal artificially infected with a TSE (transmissible spongiform encephalopathy) can be infective when inoculated intracerebrally into the same species. There have also been 4 reports of a TSE being successfully transmitted by blood transfusion in animals as follows: sheep (Houston et al 2000, Hunter et al 2002), hamsters (Rohwer 2002) and mice (Brown et al 1999), some of these studies having shown infectivity during the asymptomatic stage.

3. Infectivity appears to be present in plasma and buffy coat fractions containing white blood cells, but it may also occur in other components. Some experiments have shown significant levels of infectivity in plasma inconsistent with the hypothesis that infectivity is proportional to white cell content.

4. If it is assumed that blood from a person infected with vCJD can carry infectivity, and the level of infectivity is as suggested by the animal models, then the infectivity level in a full unit of red blood cells, platelets or plasma may be sufficient to cause infection. Patients receiving any of these products from an infected donation would therefore be at risk of infection. This conclusion seems to be valid across a wide range of assumptions regarding the infectivity of blood components.

5. The infectivity levels in certain plasma derivatives could be such that recipients of these products, if derived from an infected plasma pool, would have a risk of infection. This result is highly uncertain, and varies significantly with the assumptions made about the level of infectivity and its distribution across plasma fractions. As the size of dose, number of doses and the size of plasma pool all affect the potential risk, a calculator has been included in this report.

6. The levels of infectivity in blood components and plasma fractions have been estimated based on experiments in an animal model. The applicability of these data to vCJD infectivity in human blood is not known, but they are the best data available. Estimates of infectivity in plasma derivatives have been estimated based on two alternative approaches using the blood components and plasma fractions results.

Contents

Appendices

1. INTRODUCTION

1.1 Background

In 1997 the Spongiform Encephalopathy Advisory Committee (SEAC) reviewed the safety of blood and blood products, and recommended that the Government should consider a precautionary policy of extending the use of leucodepleted blood and blood products as far as is practicable. SEAC also recommended that risk assessments be carried out to inform decisions on any measures which may be necessary to protect recipients.

In response to this request, the Department of Health contracted Det Norske Veritas (DNV) to carry out a risk assessment study. The study evaluated the overall risk to patient groups, as well as identifying those patient groups at highest risk, and considered the benefits of measures aimed at reducing risks. The Final Report of the study was submitted to the Department of Health and SEAC in February 1999 and subsequently published.

In September 2001, the Department of Health commissioned DNV to review and update the 1999 risk assessment in light of recent experiments and research papers, with emphasis on the specific risks to patients who are known to have received blood from donors who went on to develop vCJD. This study draws heavily on the 1999 report.

It should be noted that many of the products referred to in this report are trademarked.

1.2 Objectives

The objectives of this risk assessment are:

- To update the 1999 risk assessment in the light of research papers published since 1998. However, this new study looks more specifically at risk to patients known to have received potentially contaminated blood products.
- To assess which components of blood and blood products are risk factors to human health by analysing experiments and research papers, and investigation of the processes involved in blood transfusion and the preparation and use of blood products.
- To provide a simple calculator to enable the infectivity in various plasma derivatives to be estimated. This calculator is to be used by the CJD Incidents Panel in determining the advice given to patients who are known to have received blood products prepared from a pool containing plasma from a donor who went on to develop vCJD.

2. OVERALL APPROACH

In trying to assess the risk of being infected with vCJD via blood and blood products the key question is whether the infective agent is present in blood. Whilst the evidence for infectivity in blood is reviewed (see Appendix II) ***it is not the purpose of this assessment to provide an answer to this question.*** In fact the study is based on the assumption that infectivity is present in blood.

With this in mind, the objectives of the study could be re-stated as:

On the assumption that the infective agent for vCJD is present in blood, to assess the extent of the potential exposure to vCJD infectivity, and provide a tool that enables the CJD Incidents Panel to estimate possible risks to patients known to have received plasma derivatives prepared from a pool containing plasma from a donor who went on to develop vCJD.

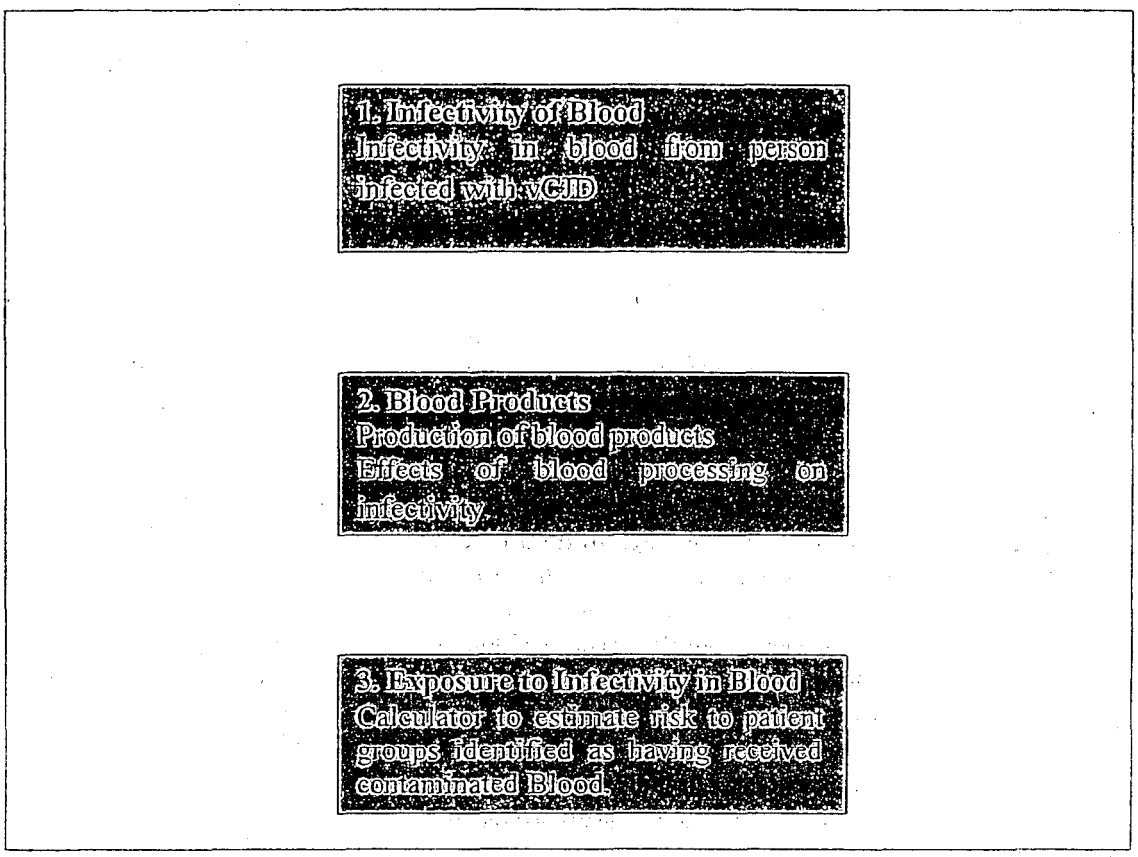
It is important to recognise that this study is not a scientific review of all the evidence concerning the potential for vCJD to be transmitted by blood. That is not our expertise. It is a risk assessment study that is intended to provide some practical insights into the possible risks from an uncertain hazard. The study has tried to assess the state of knowledge, draw assumptions based on the best scientific evidence that is available, and then to assess the range of implications from those assumptions. In this way a risk assessment can inform a decision making process, but it can never provide all the answers or consider the full range of issues that have to be weighed up in making a decision. The results of the study should not be seen as absolute estimates; they are predictions based on a set of assumptions. The value of the study lies as much in setting out those assumptions and highlighting the limitations of the data as with the quantitative results presented.

Form of Results. The main results of this assessment are presented in terms of the infectivity of blood products (per standard unit). This infectivity is then included in a calculator and the overall risk can be estimated by inputting factors such as pool size, number of doses etc.

Early drafts of this report presented three alternative approaches to estimating infectivity in plasma derivatives and the draft was sent to a range of independent experts and to 3 expert committees (Spongiform Encephalopathies Advisory Committee, the Microbiological Safety of Blood and Tissues for Transplantation and the Committee on Safety of Medicines) for comment. The consensus from these consultations was that one method was not justifiable but the remaining 2 alternative appropriate approaches could be equally defended on scientific grounds. This revised report takes into account the comments received and only considers the 2 approaches considered acceptable.

The main steps required to estimate infectivity in blood are summarised in Figure 2.1.

Figure 2.1 Overview of Risk Model



2.1 Infectivity in Blood

The first stage of the study is to consider in detail how blood is collected, processed and used. This is described in detail in Appendix I, and some of the key points summarised in Chapter 3. As already stated, this assessment is based on the premise that the infective agent for vCJD may be present in the blood of a person incubating the disease. The evidence for this is presented in Appendix II. This Appendix also presents the evidence for the choice of the amount of infectivity that may be present. This is an area for which there is considerable uncertainty.

2.2 Blood Processing and Plasma Derivatives

The various ways in which blood is separated into its main components and the plasma processed to produce plasma derivatives are summarised in Appendix I. The purpose of this is to reflect our understanding of the steps and processes involved. Many of the steps involved in producing plasma derivatives, e.g. Factor VIII, albumin etc, such as ultra-filtration and chromatography, may be effective in removing infectivity. However, it is hard to demonstrate this experimentally because it is limited by the relative insensitivity of test methods combined with the relatively low levels of infectivity found in blood in animal models (the only experimental data on the effect that blood processing beyond the initial stages may have on any infectivity present involves experiments using blood spiked with infectivity from the brain).

This report presents the two of the three alternative approaches to estimating infectivity in plasma derivatives, which the experts consulted considered scientifically sound. The other approach originally proposed is just briefly outlined. A decision on which approach to use in particular circumstances will depend on factors other than scientific merit.

The situation may change as new research results become available and the department has indicated an intention to commission regular updates to the report to take these developments into account.

2.3 Exposure to Infectivity in Blood

The final stage of the analysis is to assess the exposure risk to specific patients who are known to have received specified blood components or plasma derivatives prepared from a donor who went on to develop vCJD. The exposure risk for patients treated with such products will depend on the infectivity of the blood product or plasma derivative, the size of the dose, the number of doses and, for plasma derivatives, the size of the pool in which the blood product from the CJD donor is mixed.